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CORRESPONDENCE

Pulmonary Illness Related to E-Cigarette Use

TO THE EDITOR: We have closely followed recent publications (including the letters by Maddock et al. [Oct. 10 issue]¹ and Butt et al. [Oct. 31 issue]²) on e-cigarette, or vaping, product use–associated lung injury (EVALI), particularly the role of bronchoscopy in the diagnostic workup of this condition. It has not yet been reported how severely “routine” flexible bronchoscopy and bronchoalveolar lavage (BAL) affect pulmonary function in these patients, resulting in a highly challenging perioperative course.

We reviewed records for nine of the first patients with EVALI identified at Children’s Hospital of Wisconsin and included in the original case series described by Layden et al. (published September 6, 2019, at NEJM.org).³ Preoperatively, most patients had only moderate oxygen requirements (Table 1). Intraoperatively and postoperatively, all patients showed substantial airway reactivity, with severe coughing spells and prolonged desaturation. Four patients remained intubated. The severity of airway reactivity was disproportionate to the preoperative status and higher than what is generally anticipated.

We wish to highlight these risks and advocate limiting diagnostic bronchoscopy and BAL to settings where postoperative ventilation is readily available. In select patients, we now defer bronchoscopy and BAL when their preoperative status is tenuous or clinical findings are strongly suggestive of EVALI.

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No potential conflict of interest relevant to this letter was reported.

This letter was published on November 20, 2019, at NEJM.org.

1. Maddock SD, Cirulis MM, Callahan SJ, et al. Pulmonary lipid-laden macrophages and vaping. *N Engl J Med* 2019;381:1488-9.

2. Butt YM, Smith ML, Tazelaar HD, et al. Pathology of vaping-associated lung injury. *N Engl J Med* 2019;381:1780-1.

3. Layden JE, Ghinai I, Pray I, et al. Pulmonary illness related

to e-cigarette use in Illinois and Wisconsin — preliminary report. *N Engl J Med*. DOI: 10.1056/NEJMoa1911614.

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TO THE EDITOR: We welcome the report from Layden et al. investigating this worrisome outbreak of an inflammatory respiratory syndrome with multiorgan involvement in previously healthy persons using e-cigarettes. We agree that definitive exclusion of an infectious cause is critical in such outbreaks. However, the rates of key microbiologic investigations undertaken by the primary clinical teams were too low. These included human immunodeficiency virus testing in 27 of 53 cases, respiratory virus and atypical bacteria polymerase-chain-reaction (PCR) panels in 34 of 53, sputum cultures in 24 of 53 (it was not stated whether induced sputum sampling was pursued), and BAL-fluid culture in 18 of 24 case patients undergoing BAL. Greater emphasis must be placed on thorough microbiologic evaluation in challenging cases of suspected infection. Furthermore, we suggest that in an outbreak scenario, application of nonroutine bacterial PCR testing (including for legionella species) is warranted.¹ Emerging methods such as metagenomics should also be considered to increase diagnostic yield and ensure that a previously unknown pathogen is not missed.²⁻⁴ Early detection of an emerging or reemerging infection will require a more meticulous approach to infectious disease diagnostics.

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No potential conflict of interest relevant to this letter was reported.

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1. Gadsby NJ, Helgason KO, Dickson EM, et al. Molecular diagnosis of Legionella infections — clinical utility of front-line screening as part of a pneumonia diagnostic algorithm. *J Infect* 2016;72:161-70.

Table 1. Illness Severity in Patients with E-Cigarette, or Vaping, Product Use–Associated Lung Injury before and after Flexible Bronchoscopy and Bronchoalveolar Lavage.*

Patient No.	Preprocedure			Postprocedure					
	Oxygen Saturation	FiO ₂	Oxygen Flow Rate <i>liters/min</i>	Disposition	Oxygen Saturation on PICU Admission or End of PACU Stay %	FiO ₂ at Discharge†	Oxygen Flow Rate at Discharge† <i>liters/min</i>	Severity of Illness‡	Maximum OSI or OI§
1	99	0.7	25	ICU; intubated for 4 days	99	1.0	Patient on ventilator	Mild ARDS	OSI, 4.6
2	95	0.27	2	PACU	96	0.65	8	No ARDS	NA
3	95	Patient breathing room air	Patient breathing room air	PACU	96	0.45	4	No ARDS	NA
4	97	0.24	1	ICU; intubated for 1 day	99	1.0	Patient on ventilator	Mild ARDS	OSI, 4.2
5	95	Patient breathing room air	Patient breathing room air	PACU	93	Patient breathing room air	Patient breathing room air	No ARDS	NA
6	94	0.24	1	PACU	96	0.5	4	No ARDS	NA
7	95	0.45	3.5	PACU	98	0.45	3.5	No ARDS	NA
8	92	0.5	35	ICU; intubated for 5 days	99	1.0	Patient on ventilator	Moderate ARDS	OI, 12.6
9	91	0.8	45	ICU; intubated for 2 days	90	1.0	Patient on ventilator	Moderate ARDS	OI, 11.2

* Quality-improvement review was performed with institutional review board approval and patient consent. The mean age of the patients was 16.7 years. The patients received a general anesthetic with endotracheal tube (eight patients) or laryngeal mask airway (one patient). Perioperative oxygen was delivered through a nasal cannula, high-flow nasal cannula, or Oxygen Mask. ARDS denotes acute respiratory distress syndrome, FiO₂ fraction of inspired oxygen, ICU intensive care unit, NA not applicable, PACU postanesthesia care unit, and PICU pediatric intensive care unit.

† Discharge refers to discharge from the anesthesiologist's care.

‡ The severity of illness was determined according to the Pediatric Acute Lung Injury Consensus Conference criteria for ARDS.

§ The oxygen saturation index (OSI) is calculated as mean airway pressure in centimeters of water × FiO₂ × 100 ÷ oxygen saturation as measured by pulse oximetry. The oxygenation index (OI) is calculated as mean airway pressure in centimeters of water × FiO₂ × 100 ÷ partial pressure of arterial oxygen in millimeters of mercury.

2. Miller RR, Montoya V, Gardy JL, Patrick DM, Tang P. Metagenomics for pathogen detection in public health. *Genome Med* 2013;5(9):81.
3. Charalampous T, Kay GL, Richardson H, et al. Nanopore metagenomics enables rapid clinical diagnosis of bacterial lower respiratory infection. *Nat Biotechnol* 2019;37:783-92.
4. Wilson MR, Sample HA, Zorn KC, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. *N Engl J Med* 2019;380:2327-40.

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THE AUTHORS REPLY: Diaz et al. highlight the potential for severe airway reactivity and perioperative challenges when performing bronchoscopy and BAL in patients with EVALI, and Russell and Cevik stress the importance of ruling out infectious causes in these patients. These two points reflect the complexities of evaluating patients with EVALI and managing their care. Recent Centers for Disease Control and Prevention clinical guidance emphasizes that the decision to perform a bronchoscopy and BAL should be made on a case-by-case basis and in consultation with pulmonary specialists.¹ Many patients with EVALI have required intubation and mechanical ventilation, and consultation with critical care specialists is also recommended.

Many infectious and noninfectious illnesses can manifest with respiratory, constitutional, and gastrointestinal symptoms. Especially as the influenza season begins, clinicians must rely on a thorough initial evaluation, including history taking with respect to substance use, travel, vaccinations, and sick contacts. Laboratory testing should be performed to evaluate for multiple causes, including common infections. A chest radiograph should be obtained for patients with suspected EVALI, and a chest computed tomographic scan should be considered if the chest radiograph is normal.¹ Clinicians should strongly consider admitting patients with potential EVALI, especially if they have respiratory distress, coexisting conditions, or decreased (<95%) oxygen saturation.¹

If EVALI is suspected, a comprehensive assessment of e-cigarette, or vaping, product use habits should be conducted, including information on types of products and substances (e.g., tetrahydro-

cannabinol [THC] and nicotine) used, frequency of use, and where products were obtained. A recent study in Illinois showed that patients 18 to 44 years of age with EVALI had higher odds of obtaining products from informal sources and reporting exclusive and frequent use of THC-containing e-cigarette, or vaping, products than persons without EVALI who reported using these products.²

As of November 13, 2019, at total of 2172 EVALI cases and 42 deaths have been reported in 49 states, the District of Columbia, and the U.S. Virgin Islands. Although vitamin E acetate was recently identified in a preliminary analysis of BAL specimens,³ evidence is not yet sufficient to rule out the contribution of other toxicants. This investigation remains ongoing, and vigilant clinical evaluation, diagnosis, and management of the care of patients with EVALI are critical.

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Since publication of their article, the authors report no further potential conflict of interest.

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1. Jatlouhi TC, Wiltz JL, Kabbani S, et al. Update: interim guidance for health care providers for managing patients with suspected e-cigarette, or vaping, product use-associated lung injury — United States, November 2019. *MMWR Morb Mortal Wkly Rep* 2019 November 19 (Epub ahead of print) (https://www.cdc.gov/mmwr/volumes/68/wr/mm6846e2.htm?s_cid=mm6846e2_w).
2. Navon L, Jones CM, Ghinai I, et al. Risk factors for e-cigarette, or vaping, product use-associated lung injury (EVALI) among adults who use e-cigarette, or vaping, products — Illinois, July–October 2019. *MMWR Morb Mortal Wkly Rep* 2019; 68:1034-9.
3. Blount BC, Karwowski MP, Morel-Espinosa M, et al. Evaluation of bronchoalveolar lavage fluid from patients in an outbreak of e-cigarette, or vaping, product use-associated lung injury — 10 states, August–October 2019. *MMWR Morb Mortal Wkly Rep* 2019;68:1040-1.

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